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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/623,304
Filing Date: February 21, 2001
Appellant(s): SILVIA ET AL.

Annette S. Parent
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 01 November 2004 (hereinafter, the Brief).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect. Specifically, the response after final rejection filed on 18 August 2003 has been entered. However, this response contained no claim amendments.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct. The Examiner respectfully disagrees with Appellant's conclusion that the rejections of record (35 U.S.C. § 101, 35 U.S.C. §112, first paragraph, and 35 U.S.C. § 112, second paragraph) are improper, for reasons already made of record and re-stated herein.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-4 and 6-7 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Bork et al. Trends in Genetics. 12(10): 425-427, 1996.

Bork, A. Genome Res 10: 398-400, 2000.

Brenner, S.E. Trends in Genetics 15(4): 132-133, 1999.

Doerks et al. Trends in Genetics 14(6): 248-250, 1998.

Pessia et al. J Physiol 532(2) : 359-367, 2001.

Pessia et al. EMBO J 15(12) : 2980-2987, 1996.

Skolnick et al. Trends in Biotech 18(1): 34-39, 2000.

Smith et al. Nature Biotech 15: 1222-1223, 1997.

Tanemoto et al. J Physiol 525(3) : 587-592, 2000.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

Claims 1-4 and 6-7 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. The basis for these rejections are set forth in the previous Office Actions (23 October 2002; 16 June 2003) and is also fully set forth below.

Specifically, claim 1 is directed to an isolated nucleic acid encoding a polypeptide monomer comprising an alpha subunit of a potassium channel, the polypeptide monomer (i) forming with at least one additional Kir5.1 alpha subunit, a potassium channel having the characteristic of inward rectification, (ii) encoded by a nucleic acid molecule that selectively hybridizes under highly stringent hybridization conditions to a nucleotide sequence of SEQ ID NO: 2. Claims 2-4 also recite a nucleic acid that encodes human Kir5.1, a nucleic acid that encodes SEQ ID NO:1, and a nucleic acid that has a nucleotide sequence of SEQ ID NO: 2. Claim 6 recites that the nucleic acid encodes a polypeptide monomer having a molecular weight of about between 38kDa to 48kDa, wherein the molecular weight is predicted based on amino acid sequence. Claim 7 recites that the polypeptide monomer encoded by the claimed polynucleotide comprises an alpha subunit of a heteromeric inward rectifier potassium channel.

It is clear from the instant specification that the nucleic acid encoding the novel human Kir alpha subunit polypeptide of SEQ ID NO: 1 has been isolated because of its similarity to known proteins. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional

information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

The specification asserts that the human Kir5.1 polypeptide (SEQ ID NO: 1) encoded by the claimed nucleic acid (SEQ ID NO: 2) of the present invention is a subunit of an inward rectifier potassium channel. The specification teaches that inward rectifier channels mainly allow potassium influx, with little potassium outflux and have significant roles in maintaining the resting potential and in controlling excitability (pg 2, lines 27-28; pg 6, lines 24-25). The specification also discloses that inward rectifier potassium channels have been found in a wide variety of tissues and cell types (pg 2, lines 28-29). However, the instant specification does not teach any significance or functional characteristics of the human polynucleotide (SEQ ID NO: 2) or polypeptide (SEQ ID NO: 1). The state of the art even teaches that *rat* Kir5.1 does not belong

to any inwardly rectifying potassium channel subfamily and its physiological roles are unknown (Tanemoto et al. J Physiol 525(3): 597-592, 2000; pg 587, first paragraph). Pessia et al. also disclose that the rat Kir5.1 subunit is unusual in that it only appears to form functional potassium channels when assembled as a heteromeric channel with members of the Kir4.1 subfamily (J Physiol 532(2): 359-367, 2001; pg 359, col 1, first paragraph). Pessia et al. state that "the functional role of these heteromeric Kir4.0-Kir5.1 channels remain unclear (pg 359, col 1, 2nd paragraph). Relevant literature also discloses that "like voltage-dependent potassium channels, the molecular diversity of inwardly rectifying potassium channels may be expanded by the ability of specific subunits to form heteromeric channels with other inward rectifier subunits, producing channels with distinct characteristics" (Pessia et al. EMBO J 15(12): 2980-2987, 1996; pg 2984, first full paragraph in col 2). Since significant further research would be required of the skilled artisan to determine how the claimed polynucleotide encoding the polypeptide is involved in any activities, the asserted utilities are not substantial. Therefore, the human Kir5.1 polynucleotide and polypeptide of the instant application are not well characterized and one skilled in the art the art would not find the utility to be obvious.

It is clear from the instant specification that the human Kir5.1 polypeptide encoded by the claimed polynucleotide is what is termed an "orphan protein" in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins. There is little doubt that, after complete characterization, this DNA and protein, may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q.

689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a nucleic acid encoding a polypeptide which has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as Kir5.1, the instant invention is incomplete. In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediately obvious patentable use for it. Since the instant specification does not disclose a "real world" use for Kir5.1, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claims 1-4 and 6-7 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

Claims 1-4 and 6-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection is set forth in the previous Office Actions (23 October 2002; 16 June 2003) and is also fully set forth below.

Stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions, claims 1-4 and 6-7 fail to define the metes and bounds of the varying structures of polynucleotides recited. Specifically, the term "comprising" encompasses various unknown stringency conditions, which would allow for the stringency to be lowered before the hybridization is ended, thereby producing polynucleotide variants other than that of hKir5.1.

(11) Response to Argument

35 USC § 101 and 35 USC § 112, first paragraph

Beginning at the bottom of page 5 through page 6 of the Brief, Appellant summarizes case law on the utility requirement. Appellant's review of the issue of utility, the case law that has been cited and the holding that is found in that case law is not disputed. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility. Appellant urges that the Examiner has offered no documentary evidence or scientific basis for the conclusion that the instant Kir5.1 channel lacks specific, substantial and credible utility (page 6 of the Brief). However, Appellant is mischaracterizing the basis of the

instant rejection. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses at least one credible, specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide that would be *prima facie* obvious to the skilled artisan. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed polynucleotide encodes an ion channel, which is asserted to be specifically involved in nociception. The hypothetical specification provides the evidence by showing that alteration of the channel activity leads to the change in perception of pain. The claimed polynucleotide in the hypothetical example would not be rejected under 35 U.S.C. § 101 and § 112, first paragraph, as it has utility and is enabled as a target for pain alleviating drugs. However, such is not the fact pattern here. The instant disclosure of a novel alpha subunit of an inward rectifier potassium channel (Kir5.1) fails to provide any factual evidence that this specific Kir5.1 subunit is associated with any particular disease, condition, or physiological process other than a general regulation of cell excitability.

At page 5, at the bottom of page 6, the top of page 7, the bottom of page 8 through the middle of page 9, and at the top of page 10 of the Brief, Appellant traverses the rejection of the claims under 35 U.S.C §101 on the premises that the identification of Kir5.1 nucleic acids permits one of skill in the art to screen for modulators, activators, or inhibitors of an inward rectifier potassium channel that comprises a Kir5.1 subunit, which can be used for treating for example, hypertension, acute renal failure, chronic renal failure, diabetes insipidus, diabetic nephropathy, hypothyroidism, hyperthyroidism, goiter, hypoparathyroidism, hyperparathyroidism, pancreatic insufficiency, diabetes, cystic fibrosis, sialorrhea, and salivary

insufficiency. The asserted utility of using the Kir5.1 channel to identify modulators, activators, or inhibitors is not specific or substantial. Such assays can be performed with any polynucleotide or polypeptide, as evidenced by the general screening methods at pages 40-44 of the specification. However, the specification discloses nothing specific or substantial for the agonists, antagonists, and other modulators that can be identified by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Appellant asserts that because the Kir family of inward rectifier potassium channels is known to be involved in regulating potassium flow across the cell membrane and therefore regulate cell resting potential and excitability, one of skill in the art would expect a Kir5.1 potassium channel to play an important role in the proper physiological function of the tissues where it is expressed (the bottom of page 8 of the Brief). However, it is a matter of law that the invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention. The fact that some experimentation is required to establish the physiological role of the human Kir5.1 subunit simply confirms that the instant invention was not completed as filed, and, therefore, clearly lacks utility in currently available form. Additionally, the state of the art even teaches that *rat* Kir5.1 does not belong to any inwardly rectifying potassium channel subfamily and its physiological roles are unknown (Tanemoto et al. J Physiol 525(3): 597-592, 2000; pg 587, first paragraph). Pessia et al. also disclose that the rat Kir5.1 subunit is unusual in that it only appears to form functional potassium channels when assembled as a heteromeric channel with members of the Kir4.1 subfamily (J Physiol 532(2): 359-367, 2001; pg 359, col 1, first paragraph). Pessia

et al. state that "the functional role of these heteromeric Kir4.0-Kir5.1 channels remain unclear (pg 359, col 1, 2nd paragraph). Relevant literature also discloses that "like voltage-dependent potassium channels, the molecular diversity of inwardly rectifying potassium channels may be expanded by the ability of specific subunits to form heteromeric channels with other inward rectifier subunits, producing channels with distinct characteristics" (Pessia et al. EMBO J 15(12): 2980-2987, 1996; pg 2984, first full paragraph in col 2).

Furthermore, based on the statement that modulators of potassium channels comprising a Kir5.1 subunit are useful for treating conditions and diseases related to altered cell excitability in tissues where Kir5.1 is expressed (e.g. hypertension, acute renal failure, chronic renal failure, diabetes insipidus, diabetic nephropathy, hypothyroidism, hyperthyroidism, goiter, hypoparathyroidism, hyperparathyroidism, pancreatic insufficiency, diabetes, cystic fibrosis, sialorrhea, and salivary insufficiency) (page 6 through the top of page 7 and page 8 through page 10 of the Brief), one would not know what effect to expect if a modulator, an antagonist or an agonist of the Kir5.1 subunit is administered to a patient because the *specific* physiological role of the subunit channel is not disclosed. Additionally, the specification of the instant application discloses nothing about the normal levels of expression of the Kir5.1 polynucleotide. The specification does not disclose specific disorders or conditions associated with the Kir5.1 gene, either normal or mutated/deleted/translocated. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease or condition. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial. Moreover, a skilled practitioner would not reasonably expect administration of potential modulators of Kir5.1 to have any effect on any of

the diseases that alter cell excitability. It is noted that the specification of the instant application teaches that human Kir5.1 is expressed in various tissues, including pancreas, thyroid gland, salivary gland, and kidney (page 58 of the specification). However, the asserted utility of tissue typing for human Kir5.1 is not substantial because one skilled in the art would not readily use the protein in tissue-typing in a real world sense since the protein is not specific to one tissue and is not associated with any disease or disorder. Table 1 (Example III, page 58 of the specification) does not indicate any qualitative/numerical results or any controls, such that it is not clear if the expression of Kir5.1 is statistically significant. Furthermore, this asserted utility is not specific because numerous unrelated proteins would also show a similar tissue typing pattern. Evidence of mere expression of the protein in a tissue is not tantamount to a showing of a role of the Kir5.1 DNA or protein in hypertension, acute renal failure, chronic renal failure, diabetes insipidus, diabetic nephropathy, hypothyroidism, hyperthyroidism, goiter, hypoparathyroidism, hyperparathyroidism, pancreatic insufficiency, diabetes, cystic fibrosis, sialorrhea, and salivary insufficiency.

It is clear from the instant application that the human Kir5.1 subunit DNA of the instant invention has been isolated because of its similarity to known DNA molecules encoding known proteins. At the time of filing of the instant application, the biological significance of the DNA encoding the Kir5.1 potassium channel subunit protein was not known. The state of the art even teaches that *rat* Kir5.1 does not belong to any inwardly rectifying potassium channel subfamily and its physiological roles are unknown (Tanemoto et al. J Physiol 525(3): 597-592, 2000; pg 587, first paragraph). Pessia et al. also disclose that the rat Kir5.1 subunit is unusual in that it only appears to form functional potassium channels when assembled as a heteromeric channel

with members of the Kir4.1 subfamily (J Physiol 532(2): 359-367, 2001; pg 359, col 1, first paragraph). Pessia et al. state that "the functional role of these heteromeric Kir4.0-Kir5.1 channels remain unclear (pg 359, col 1, 2nd paragraph). Relevant literature also discloses that "like voltage-dependent potassium channels, the molecular diversity of inwardly rectifying potassium channels may be expanded by the ability of specific subunits to form heteromeric channels with other inward rectifier subunits, producing channels with distinct characteristics" (Pessia et al. EMBO J 15(12): 2980-2987, 1996; pg 2984, first full paragraph in col 2). Because the specific physiological function of Kir5.1 was not disclosed, administration of pharmaceutical agents targeting Kir5.1 would be meaningless without further characterization of Kir5.1 to identify its specific significance, which would lead to a specific and substantial credible utility of Kir5.1. This further characterization, however, is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to

engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Beginning at page 9 through page 10 of the Brief, Appellant attempts to indicate what constitutes a specific, substantial and credible utility of human Kir5.1 polynucleotide and amino acid sequences. Appellant submits that the present invention has a specific utility, namely that the human Kir5.1 channels can mediate potassium influx in, e.g. kidney, thyroid gland, or pancreas, which is clearly specific for the claimed Kir5.1 channels and not any ion channels. At the bottom of page 10 of the Brief, Appellant also argues that the asserted utility of the Kir5.1 channel relies on the results of the assays confirming the functional characteristics of an inward rectifier potassium channel (Examples I-III of the specification). However, it is well known in the art of general biology that all living cells have plasma membranes and have an electric charge difference across their membranes. It is also a general knowledge that renal tubule cells, β-cells, and thyroid cells (for example) have the ability to generate changes in their membrane potentials due to the presence of membrane ion channels, therefore, these cells are called excitable cells. The state of the art even teaches that *rat* Kir5.1 does not belong to any inwardly rectifying potassium channel subfamily and its physiological roles are unknown (Tanemoto et al. J Physiol 525(3): 587-592, 2000; pg 587, first paragraph). Thus, the identification of human Kir5.1 as a novel channel that modulates cell excitability does not substantiate the specific utility for the claimed molecules because is not disclosed to be associated with any specific function any further than general regulation of a membrane potential.

Appellant asserts further that the present invention has a real-world use in the

modulation of the physiology of tissues in which Kir5.1 is expressed, as well as in the identification of compounds that modulate Kir5.1 channels (page 11 of the Brief). The Examiner maintains that the asserted utility of the Kir5.1 subunit as a modulator of cell excitability is not a substantial utility because it relates to the protein for which no biological significance is disclosed. To use the instant claimed Kir5.1 nucleic acids for the identification of compounds that modulate Kir5.1 channels is clearly to use them as an object of future research to further discover which physiological effect would be associated with the modulation of the Kir5.1 channel and the physiology of the tissues expressing Kir5.1.

Appellant argues that the artisan can readily use the Kir5.1 polypeptide to form a heteromeric potassium channel and is evidenced by Example II and Figure 1 (page 12 of the Brief). The Examiner acknowledges that based upon the results disclosed in Figure 1 (Example II) of the specification, one skilled in the art would reasonably recognize the instant Kir5.1 polypeptide as a potassium channel subunit protein. However, basic research is still required to study the properties and activity of the claimed human Kir5.1 polynucleotide that encodes the polypeptide of SEQ ID NO: 1. The specification of the instant application does not disclose the specific biological function of the polynucleotide and polypeptide. The fact that some experimentation is required to establish the physiological role of the human Kir5.1 subunit simply confirms that the instant invention was not completed as filed, and, therefore, clearly lacks utility in currently available form. Additionally, the state of the art even teaches that *rat* Kir5.1 does not belong to any inwardly rectifying potassium channel subfamily and its physiological roles are unknown (Tanemoto et al. J Physiol 525(3): 597-592, 2000; pg 587, first paragraph). Pessia et al. also disclose that the rat Kir5.1 subunit is unusual in that it only appears

to form functional potassium channels when assembled as a heteromeric channel with members of the Kir4.1 subfamily (J Physiol 532(2): 359-367, 2001; pg 359, col 1, first paragraph). Pessia et al. state that "the functional role of these heteromeric Kir4.0-Kir5.1 channels remain unclear (pg 359, col 1, 2nd paragraph). Relevant literature also discloses that "like voltage-dependent potassium channels, the molecular diversity of inwardly rectifying potassium channels may be expanded by the ability of specific subunits to form heteromeric channels with other inward rectifier subunits, producing channels with distinct characteristics" (Pessia et al. EMBO J 15(12): 2980-2987, 1996; pg 2984, first full paragraph in col 2). Therefore, the human Kir5.1 polynucleotide and polypeptide of the instant application are not well characterized and one skilled in the art the art would not find the utility to be obvious.

At page 12 of the Brief, Appellant asserts that the specification discloses the normal expression levels of Kir5.1 polynucleotide in various tissues (pg 58 of the specification). Appellant also contends that the specification names a large number of diseases and conditions that can be treated by modulators of Kir5.1 channels, which clearly provides a real world use of the modulators and thus the Kir5.1 nucleic acid or polypeptide. Although the specification teaches the expression of human Kir5.1 in various tissues, one skilled in the art would not readily use the polynucleotide or protein for tissue typing in a real world sense because the polynucleotide and protein are not specific to one tissue and are not associated with any disease or disorder. Additionally, Table 1 (Example III, page 58 of the specification) does not indicate any qualitative/numerical results or any controls, such that it is not clear if the expression of Kir5.1 is statistically significant. Numerous other unrelated polynucleotides and proteins would also show a similar tissue typing pattern. Evidence of mere expression in a tissue is not

tantamount to a showing of a role in hypertension, acute renal failure, chronic renal failure, diabetes insipidus, diabetic nephropathy, hypothyroidism, hyperthyroidism, goiter, hypoparathyroidism, hyperparathyroidism, pancreatic insufficiency, diabetes, cystic fibrosis, sialorrhea, and salivary insufficiency. The specification of the instant application does not disclose specific disorders or conditions associated with the Kir5.1 gene, either normal or mutated/deleted/translocated. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease or condition. One skilled in the art would not know what effect to expect if a modulator, an antagonist or an agonist of the Kir5.1 subunit is even administered to a patient because the *specific* physiological role of the subunit/channel is not disclosed. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Appellant's assertion of credible utility, as presented on page 10-11 and 12-13 of the Brief, is not and has never been disputed by the Examiner. There is no disagreement that based on the information provided in the instant specification, as filed, one skilled in the art would reasonably recognize the instant Kir5.1 polypeptide as a potassium channel subunit protein. As such, the Kir5.1 channel could be involved in modulating cellular excitability. However, one readily recognizes that any excitable cell, such as a renal tubule cell, β-cell, or thyroid cell, normally expresses a significant number of cation channels, which are involved in modulating excitability. Therefore, asserted utility of Kir5.1 channel as a modulator of cell excitability is not specific because it is associated with a general physiological function of regulating a membrane potential in a cell.

At page 13 of the Brief, Appellant expresses an opinion that the Examiner

maintains the utility rejection based on personal disbelief of the asserted utility rather than credible scientific evidence. Appellant submits that the specification (Example II, Figure 1) shows that Kir5.1 and Kir4.1 can form a heteromeric potassium channel. The Examiner acknowledges that based upon the results disclosed in Figure 1 (Example II) of the specification, one skilled in the art would reasonably recognize the instant Kir5.1 polypeptide as a potassium channel subunit protein. However, basic research is still required to study the properties and activity of the claimed human Kir5.1 polynucleotide that encodes the polypeptide of SEQ ID NO: 1. The specification of the instant application does not disclose the specific biological function of the polynucleotide and polypeptide. The fact that some experimentation is required to establish the physiological role of the human Kir5.1 subunit simply confirms that the instant invention was not completed as filed, and, therefore, clearly lacks utility in currently available form. Appellant refers to the appropriate utility sections of MPEP § 2107.02, which places the initial burden on the Examiner, not Appellant, to provide evidence to support factual conclusion of the credibility of an asserted utility (at page 14 of the Brief). These arguments are not found to be persuasive. The Examiner's position, as clearly put forth in the Office Actions of record, is solely based on the analysis of factual evidence presented in the instant specification, as filed. As such, based on the sequence similarity of the novel nucleic acid molecules of the instant invention to known sequences of inward rectifying potassium channels and the current modulation of Kir5.1 disclosed in Example II of the specification, it can be concluded that the instant Kir5.1 channel could be a novel inward rectifying potassium channel subunit protein. Therefore, one skilled in the art would not doubt that Kir5.1 channel could be involved in modulating cellular excitability because that is one of the major known and

established functions of ion channels. However, the asserted utility of the Kir5.1 channel as a modulator of cell excitability is not specific or substantial because these utilities relate to a general physiological of regulating a membrane potential in an excitable cell. The Kir5.1 protein encoded by the claimed nucleic acid of the instant invention belongs to a family of compounds generally related to the most general physiological mechanism, such as cellular excitability. The utility of those members of the inward rectifying potassium channels to which the claimed protein in the instant application appears to belong lies in the knowledge that they modulate a specific physiological activity in response to a specific signal. Since the instant specification does not disclose the identity of the signal or a specific physiological pathway in the connection with any process which one would wish to manipulate for a desired clinical effect, screening for agonists or antagonists of the pathway through which that ion channel transduces its signal in response to that signal is not particularly useful.

Appellant's reliance on *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980) is not found to be persuasive (pages 15-16 of the Brief). In *Nelson v. Bowler*, the court reversed a finding by the Office that the applicant had not set forth a "practical" utility under 35 U.S.C. § 101, and stated: "Practical utility is a shorthand way of attributing "real-world" value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public". In the instant case, assertions that "[b]ecause abnormal ion influx can interfere with the normal physiological functions of organ and tissues, compounds capable of modulating ion channels, such as Kir5.1 channels, are useful as therapeutic agents for treating these conditions" (the top of page 16 of the Brief) clearly establish that the instant invention cannot be used "in a manner which provides

some immediate benefit to the public". To grant Appellant a patent encompassing isolated nucleic acid molecules encoding a naturally occurring human protein, which is not readily usable in its current form, would be to grant Appellant a monopoly "the metes and bounds" of which "are not capable of precise delineation". That monopoly "may engross a vast, unknown, and perhaps unknowable area" and "confer power to block off whole areas of scientific development, without compensating benefit to the public" (*Brenner v. Manson, Ibid*). To grant Appellant a patent on the claimed polynucleotide based solely upon an assertion that it encodes a protein that can be employed for screening agonists or antagonists to modulate cell excitability (potassium influx) to treat various diseases and disorders is clearly prohibited by this judicial precedent since the compensation to the public is not commensurate with the monopoly granted.

Claims 1-4 and 6-7 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

35 USC § 112, second paragraph

Beginning at page 17 of the Brief, Appellant summarizes the statutory requirements under 35 U.S.C. § 112, second paragraph and cites MPEP § 2173. Appellant's review of the issue of definiteness under 35 U.S.C. § 112, second paragraph is not disputed. The essential disagreement appears to be the interpretation of what constitutes a definite claim.

Appellant asserts that the hybridization conditions recited in claim 1 would allow one of skill in the art to properly determine the metes and bounds of the claimed invention (the bottom of page 18 of the Brief). Appellant states that two references, Roche Applied Science product manual and *Molecular Cloning: A Laboratory Manual*, were submitted along with a communication to the PTO to support this position. Specifically, Appellant argues that the Roche manual describes the main factors that can effects nucleic acid hybridization stringency: temperature, pH, monovalent cations (such as Na^+ in SSC and SDS), and formamide. Appellant adds that among these factors, the manual indicates that pH has little effect on hybridization when in the range of 5-9 and that Na^+ concentrations above 0.4M in a hybridization solution have only very slight effect on hybridization stringency (see the bottom of page 18 through the top of page 19 of the Brief). Appellant argues that claim 1 recites specific hybridization and wash temperatures as well as a specific concentration of formamide. Appellant indicates that the claimed hybridization solution has a Na+ concentration above 0.4M and that even if additional monovalent cations are included in the hybridization solution, the level of stringency will not be significantly effective. Appellant's arguments have been fully considered but are not found to be persuasive. Specifically, the Examiner has interpreted the terms "comprise and comprising" as open-ended claim language that does not exclude additional, unrecited elements or steps (see, *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct

within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). In the absence of a recitation of clear hybridization conditions, claims 1-4 and 6-7 fail to define the metes and bounds of the varying structures of polynucleotides recited. For example, the terms "comprise and comprising" encompass various unknown stringency conditions, which would allow for the stringency to be lowered before the hybridization is ended, thereby producing polynucleotide variants other than that of human Kir5.1. Additionally, the terms "comprise and comprising" encompass low stringency washes, which may not remove the polynucleotide variants associated with non-specific hybridization. For example, the higher the salt concentration and the lower the wash temperature, the less stringent the wash (see Roche manual pg 33, col 2; pg 35, col 2, second paragraph). The Roche Applied Science product manual even teaches that "during hybridization, duplexes form between perfectly matched sequences and between imperfectly matched sequences. The extent to which the latter occurs can be manipulated to some extent by varying the stringency of the hybridization reaction" (pg 35, col 2, first paragraph).

At the bottom of page 19 through page 20 of the Brief, Appellant asserts that besides reciting hybridization conditions, which provides a structural limitation of the claimed nucleic acid, claim 1 also recites a functional limitation of the claimed Kir5.1 nucleic acid: the nucleic acid encodes a polypeptide monomer comprising an alpha subunit of a potassium channel and that the potassium channel has the characteristic of inward rectification. Appellant argues that the specification describes assay methods for assessing the functionality of an inward rectifier

potassium channel (Example II), such that one of skill in the art would be able to examine the functional characteristics of a polypeptide and determine whether the coding polynucleotide sequence for this polypeptide is within the scope in the functional aspect. At the top of page 20 of the Brief, Appellant contends that the art in the field of electrophysiology is highly advanced and various methods for functional verification of an inward rectifier potassium channel are known to those skilled in the art. Although Appellant asserts that the recitation of hybridization conditions is a structural limitation, the term "comprise or comprising" is reasonably interpreted by the Examiner as hybridization at those conditions recited in the claims followed by re-hybridization at low or minimal stringency, which thereby produce polynucleotide variants other than that of Kir5.1. The specification of the instant application teaches that nucleic acids also hybridize under moderately stringent hybridization conditions and that "those of ordinary skill in the art will readily recognize that alternative hybridization and wash conditions can be utilized to provide conditions of similar stringency" (pg 21, lines 17-18 and 21-22). Therefore, the claims do not recite meaningful structural limitations and one of skill in the art would not be apprised of the metes and bounds of the hybridization conditions and the varying structures of the polynucleotides produced.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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